REMARKS

Claims 1, 2, 4, 6, 8-12, 50, 51, 53-55, 57, 58, and 61-75, 78-84, and 87-112 were pending in this application. Claims 6, 50, 51, 53, 57, 65, 66, 90, 91, 92, 95 and 102 have been amended and claims 4 and 89 have been cancelled. In addition, the Examiner has indicated that claims 87-112 stand withdrawn from further consideration as being drawn to a non-elected invention. Accordingly, upon entry of this amendment, claims 1, 2, 6, 8-12, 50, 51, 53-55, 57, 58, 61-75, 78-84, 87, 88, and 90-112 will be pending.

The Examiner has indicated that claims 4, 6, and 53 are free of the art and that claims 1-2 and 8-12 are allowed.

No new matter has been added. Any amendment and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was performed solely in the interest of expediting prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Support for the claim amendments and the new claims presented herein may be found throughout the specification and claims, as originally filed. Specifically, support the amendments to claims 57 and 102 may be found at, for example, page 37, lines 27-31 of the specification; and support for the amendments to claims 6, 51, 53, 90, 91, and 92 to recite "induces IFN-γ production", may be found at, for example, page 14, lines 32-33 of the specification.

No additional search is required and no new issues have been raised by the amendments made herein; support for the amendments made can be found in the specification as filed and/or in the claims as previously pending. Furthermore, in view of the amendments and arguments set forth herein, the number of issues for appeal have been reduced. It is believed that the Examiner's rejections under §112, first paragraph and §112, second paragraph have been obviated by claim amendments and cancellations. With respect to the Examiner's rejection under §112, first paragraph of claims 6 and 53, and claims dependent therefrom, for the recitation of the term "modulates", Applicants submit that as the generic term "modulates", which embraces the terms "induces" and reduces" has already been searched, it is Applicants understanding that the term "induces" will not require further search. Therefore, the claim amendments and cancellations made herein are permissible under 37 C.F.R. §1.116 as reducing

the number of issues for appeal, and Applicants respectfully request that the present Amendment be entered.

The specification has been amended to correct reference to a trademark as required by the Examiner in co-pending application no: 11/291,426.

Withdrawal of Certain Objections/Rejections

Applicants gratefully acknowledge the Examiner's indication that the following objections/rejections have been withdrawn:

the objection to the specification for lack of sequence compliance under C.F.R. § 1.821-1.825;

the rejection of claims 50 and 64 under 35 U.S.C. §112, second paragraph, as being indefinite for the recitation of "differentiating Thp cells and Th2 cells into Thl cells";

the rejection of claim 58 under 35 U.S.C. §112, second paragraph, as being indefinite for the recitation of "comprising at least 700 nucleotides which is complementary to SEQ ID NO:1",

the rejection of claims 1, 2, 4, 6, 8-12, 50-51, 53-58, and 61-86 under 35 U.S.C. § 112, first paragraph, as it pertains to lack of written description for "complements";

the rejection of claims 54, 76, and 77 under 35 U.S.C. §112, first paragraph, new matter, for the recitation of "heterologous polypeptide."; and

the rejection of claims 1, 2, 8, 10, 51, 55, 58, 67, and 69 under 35 U.S.C. § 102(b) as being anticipated by Bulfone, *et al.* (1995) *Neuron* 15:63-78.

Rejection of Claim 57Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained the rejection of claim 57 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." "This is a new matter rejection." More specifically, the Examiner is of the opinion that

> claim 57, as amended, depends from claim 51, which recites an isolated nucleic acid molecule which hybridizes to the complement of SEQ ID

> NO: 1 over the full length. Therefore, the disclosure of labeled "probes" does not provide adequate support for the instant claim. Furthermore, the only recited examples of said probes are SEQ ID NO: 1 and 3, and the instant claim is drawn a nucleic acid molecules that hybridizes to the "complement of" SEQ ID NO:1.

Applicants respectfully traverse the foregoing rejection for the reasons of record, however, without acquiescing to the validity of the Examiner's rejection and solely in the interest of expediting examination, Applicants have amended claim 57 such that it is directed to ***isolated nucleic acid molecules comprising the nucleotide sequence shown in SEQ ID NO:1, wherein the nucleic acid molecule is labeled with a detectable substance.*** As indicated by the Examiner, "the specification discloses labeled nucleic acid probes that hybridize to T-bet mRNA, including probes such as the T-bet DNA of SEQ ID NO: 1 or 3" (see, for example, the Office Action dated March 22, 2006, at page 4, seventh full paragraph). Accordingly, Applicants request reconsideration and withdrawal of this §112, first paragraph rejection of claim 57.

Rejection of Claim 4, 6, 50, 53, 64-75, and 78-84 Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained the rejection of claims 4, 6, 50, 53, 64-75, and 78-84 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention." More specifically, the Examiner is of the opinion that

> there is insufficient written description to demonstrate that applicant was in possession of the claimed genus of nucleic acids that are "90% identical with SEQ ID NO:1", "encodes a polypeptide 95% identical to SEQ ID NO: 2", or "a fragment of at lest 700 contiguous nucleotides of SEQ ID NO: 1" .

The Examiner is further of the opinion that

> [w]ith regard to claim 53, while the claim recites an isolated nucleic acid molecule which encodes a polypeptide with "95% identity", the recited function of said polypeptide is that it binds to a T-box site in DNA and "modulates" IFN-γ production. Therefore, the instant claims encompass a genus of nucleic acid molecules that are capable of "modulating" IFN- γ. For

> example, the claims might encompass nucleic acid molecules that can increase or decrease IFN- γ (i.e. "modulate"). The claims might even encompass nucleic acids that turn IFN- γ on or off, or those that result in intermittent modulation. In contrast, ***Applicant has only described nucleic acid molecules that induce IFN-γ production***. (Emphasis added).

With respect to claim 4, cancellation of this claim has rendered the Examiner's rejection moot. With respect to the Examiner's rejection to claims 6 and 53, and claims dependent therefrom, for the recitation of "modulates IFN-γ production", the amendments to the claims to recite "induces IFN-γ production" renders this portion of the Examiner's rejection moot.

With respect to the Examiner's rejection of claims 6 and 53, and claims dependent therefrom, for the recitation of nucleic acids that are "90% identical with SEQ ID NO:1" and "encodes a polypeptide 95% identical to SEQ ID NO: 2", respectively, Applicants respectfully traverse the aforementioned rejection for the reasons of record as well as the reasons set forth below.

Claim 6 is directed to isolated nucleic acid molecules which have at least ***90% nucleotide identity with SEQ ID NO:1 over its full length, and which encode a polypeptide that binds a consensus T-box site in DNA and induces IFN-γ production***. Claim 53 is directed to isolated nucleic acid molecules which encode ***a polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:2, wherein said nucleic acid molecules encode a polypeptide that binds to a consensus T-box site in DNA and induces IFN-γ production***. Applicants respectfully submit that there is sufficient written description in Applicants' specification regarding the claimed nucleic acid molecules, to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by section 112, first paragraph (see M.P.E.P. §2163.02).

As the Examiner is aware, the Federal Circuit has addressed the sufficiency of a disclosure in meeting the written description requirement of 35 U.S.C. §112 for claims to a genus of cDNAs. Specifically, the Federal Circuit stated that

> [a] description of a genus of cDNAs may be achieved by means of a recitation of ***a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or a recitation of structural features common to the members of the***

> ***genus, which features constitute a substantial portion of the genus*** [*emphasis added*].

The Regents of the University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Accordingly, it is well settled that a claim to a genus of compounds satisfies the written description requirement if the specification *either* defines a representative number of its members falling within the scope of the genus by disclosing the sequence *or* if the specification defines the structural features common to a substantial portion of the genus. It is Applicant's position that the instant specification meets the written description requirements articulated by the Federal Circuit in Eli Lilly.

Applicants respectfully submit that the claimed genus of isolated nucleic acid molecules, which have at least 90% nucleotide identity with SEQ ID NO:1 over its full length, and which encode a polypeptide that binds a consensus T-box site in DNA and induces IFN-γ production and the claimed genus of nucleic acid molecules which encode a polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:2, wherein said nucleic acid molecules encode a polypeptide that binds to a consensus T-box site in DNA and induces IFN-γ production are ***defined by structural and functional features that are described in the specification, recited in the claims, and commonly possessed by its members***.

In particular, *the structure of the claimed genus* is taught in the specification, *i.e.*, the sequence, of the nucleic acid molecules of the invention (SEQ ID NO:1) as well as the structure, *i.e.*, the sequence, of the polypeptide encoded by this nucleic acid molecule (SEQ ID NO:2). Applicants have also provided *functional features common to the claimed genus* of nucleic acid molecules, *i.e.*, the claimed nucleic acid molecules encode polypeptides that bind to a consensus T-box site in DNA and induce IFN-γ production.

Applicants further wish to point out that they have disclosed the amino acid sequence of human (SEQ ID NO:2) and murine (SEQ ID NO:4) T-bet polypeptides as well as the nucleotide sequence of human (SEQ ID NO:1) and murine (SEQ ID NO:3) T-bet nucleic acid molecules. In particular, the mouse T-bet nucleic acid molecule identified in Example 1 at page 62, line 28, through page 29, lines 1-25 was used to identify the human T-bet nucleic acid molecule. Human T-bet nucleic acid molecules share 85.7% nucleotide identity over their full length with murine T-bet nucleic acid molecules. Therefore, Applicants have disclosed a nucleic acid molecule

comprising a nucleotide sequence having slightly less than 90% nucleotide identity to SEQ ID NO:1 and a nucleic acid molecule comprising a nucleotide sequence having slightly less than 90% nucleotide identity to SEQ ID NO:3. (See, *e.g.,* Appendix A, submitted herewith, and Figures 1A-1B of the specification).

Furthermore, Applicants specification teaches methods routine to one of skill in the art to identify additional T-bet nucleic acid molecules (see, *e.g.,* page 15, line 34, through page 16, lines 1-17) and natural allelic variants of T-bet (see, *e.g.,* page 16, lines 27, through page 17, lines 1-5), and T-bet DNA sequence polymorphisms (see, *e.g.,* page 16, lines 18-26 of the specification).

Furthermore, both the human and murine T-bet nucleic acid molecules, even though they are slightly less than 90% identical to each other at the nucleotide level, encode polypeptides that have a specific function taught in the specification, recited in the claims, and commonly possessed by the members, *i.e.,* bind to a consensus T-box site in DNA and induce IFN-γ production.

Hence, Applicants should be entitled to claim nucleic acid molecules having an even higher percentage identity to the human and murine T-bet reference nucleic acid molecules with a specific function, *i.e.,* a polypeptide comprising an amino acid sequence at least 90% identical to SEQ ID NO:1 over its full length which encodes a polypeptide binds a consensus T-box site in DNA and induces IFN-γ production.

Similarly, with respect to T-bet polypeptides, since human T-bet polypeptides share 86.9% amino acid identity with murine T-bet polypeptides, Applicants have disclosed a polypeptide comprising an amino acid sequence having slightly less than 95% amino acid identity to SEQ ID NO:2 and to a polypeptide comprising an amino acid sequence having slightly less than 95% amino acid identity to SEQ ID NO:4. (See, *e.g.,* Appendix B, submitted herewith, and Figures 1C-1F of the specification).

In addition, the specification at, for example, page 28, lines 25-35, teaches domains that are conserved among members of T-bet polypeptide. For example, as indicated in the specification, the conserved domains and amino acid residues, *e.g.*, an amino-terminal portion of T-bet that includes a T-box domain at least amino acids 138-327 of human T-bet or at least

amino acids 137-326 of mouse T-bet), a tyrosine phosphorylation site (amino acids 324-366 and/or 523-534 of human T-bet or amino acids 323-335 or 518-529 of murine T-bet), and a nuclear localization sequence (amino acids 498-501 of human T-bet or 493-496 of murine T-bet), are domains that may be present in T-bet polypeptides.

Applicants have also disclosed assays in the specification that one of skill in the art may use to test whether these T-bet polypeptides binds to and transactivate a T-box consensus site in DNA and induce IFN-γ production (see, *e.g.,* page 64, lines 15-35 and page 67, line19, through page 68, lines 1-26 of the specification).

Furthermore, both human and murine T-bet, even though they are slightly less than 95% identical to each other at the amino acid level, have a specific function taught in the specification, recited in the claims, and commonly possessed by the members, *i.e.,* bind to a consensus T-box site in DNA and induce IFN-γ production.

Therefore, Applicants should be entitled to claim nucleic acid molecules which encode polypeptides having at least 95% identity to the human and murine T-bet reference nucleic acid molecules and amino acid sequences which encode a polypeptide that binds a consensus T-box site in DNA and induces IFN-γ production, since Applicants have demonstrated that polypeptides having 86.9% identity share this function.

Based on all of the foregoing, Applicants respectfully submit that there is sufficient written description in Applicants' specification regarding the claimed nucleic acid molecules and polypeptides encoded by such nucleic acid molecules, to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by section 112, first paragraph (see M.P.E.P. §2163.02).

With respect to the Examiner's assertion that "claim 4 and 6 of the instant application are directed to a nucleic acid molecule that is '90% identical' with SEQ ID NO:1, and therefore do not meet the limitations of the written description guidelines cited by Applicant", Applicants respectfully submit that the 95% limitation recited in Example 14 of the *Revised Interim Written Description Guidelines Training Materials* is not meant to limit Applicants to nucleic acid molecules that are 95% identical, but rather serves as a guideline in establishing whether disclosure of ***a single species of nucleic acid molecules*** complies with the requirement of

written description "through disclosure of relevant identifying characteristics, *i.e.*, structure, other physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, First Paragraph Written Description Requirement.*

As discussed above, Applicants have provided such structural (*i.e.*, sequence) and functional characteristics. Furthermore, Applicants have identified nucleotide and amino acid differences in the disclosed murine and human sequences which maintain the required function and thus, have provided guidance as to which amino acid changes in the reference sequence may be made.

In further support of Applicants position that the *Revised Interim Written Description Guidelines Training Materials* are not meant to limit Applicants to nucleic acid molecules with 95% identity and a recited function, Applicants submit that the U. S. Patent Office has recognized that nucleic acid molecules with 90% identity and a recited function are patentable (see, for example, United States Patents 6,331,423, 6,818,427, and 6,664,077, attached as Appendices C, D, and E, respectively). Accordingly, the fact that the *Revised Interim Written Description Guidelines Training Materials* recites 95% nucleic acid identity does not in any way imply that the claimed nucleic acid molecules which have at least 90% nucleotide identity with SEQ ID NO:1 over its full length, and which encode a polypeptide that binds a consensus T-box site in DNA and induces IFN-γ production and/or nucleic acid molecules which encode a polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:2, wherein said nucleic acid molecules encode a polypeptide that binds to a consensus T-box site in DNA and induces IFN-γ production are inadequately described.

Based on all of the above, Applicants submit that one of skill in the art would conclude that Applicants were in possession of the claimed invention at the time of filing and thus, Applicants have fulfilled the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

NEW GROUNDS OF REJECTION

Rejection of Claims 4, 6, 50-51, 53, 57, 64-75, and 78-84
Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 4, 6, 50-51, 53, 57, 64-75, and 78-84 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular the Examiner is of the opinion that the claims "are indefinite in the recitation of a nucleic acid encoding a polypeptide that 'modulates' IFN-γ production."

With respect to claim 4, cancellation of this claim has rendered the Examiner's rejection moot. With respect to claims 6, 51, 53, and claims dependent therefrom, Applicants submit that the amendment to claims 6, 51, and 53 render the Examiner's rejection moot. In particular, Applicants have amended claims 6, 51, and 53 to recite "***induces IFN-γ production***". As indicated by the Examiner in sections 9 and 12 of the instant Office Action, Applicants have described "nucleic acid molecules that *induce* IFN-γ production" and that the instant specification discloses on page 14 that T-bet *induces* IFN- γ production." Accordingly, Applicants request reconsideration and withdrawal of this §112, second paragraph rejection of claims 4, 6, 50-51, 53, 57, 64-75, and 78-84.

Rejection of Claims 4, 6, 50-51, 53, 57, 64-75, and 78-84
Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 4, 6, 50-51, 53, 57, 64-75, and 78-84 under 35 U.S.C. §112, first paragraph, "as not contain[ing] a written description of the claimed invention." "This is a new matter rejection." In particular the Examiner is of the opinion that

> [t]he instant specification does not disclose nucleic acid molecules encoding polypeptides that "modulate" IFN-y, as now claimed.

With respect to claim 4, cancellation of this claim has rendered the Examiner's rejection moot. With respect to claims 6, 51, 53, and claims dependent therefrom, Applicants submit that the amendment to claims 6, 51, and 53 render the Examiner's rejection moot. In particular, Applicants have amended claims 6, 51, and 53 to recite "***induces IFN-γ production***". As indicated by the Examiner in sections 9 and 12 of the instant Office Action, Applicants have described "nucleic acid molecules that *induce* IFN-γ production" and that the instant specification discloses on page 14 that T-bet *induces* IFN- γ production." Accordingly, Applicants request

reconsideration and withdrawal of this §112, first paragraph rejection of claims 4, 6, 50-51, 53, 57, 64-75, and 78-84.

Rejection of Claims 4, 6, 50-51, 53, 57, 64-75, and 78-84
Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claim 4, 6, 50-51, 53, 57, 64-75, 78-84 under 35 U.S.C. § 112, first paragraph because, according to the Examiner,

> the specification, while being enabling for a polypeptide that has the activity of inducing IFN-y production in $CD4^+$ cells, does not reasonably provide enablement for a polypeptide that "modulates IFN-y production".

With respect to claim 4, cancellation of this claim has rendered the Examiner's rejection moot. With respect to claims 6, 51, 53, and claims dependent therefrom, Applicants respectfully traverse the foregoing rejection and submit that one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation. However, in an effort to expedite examination and in no way acquiescing to the Examiner's rejection, Applicants have amended claims 6, 51, 53. Specifically, claims 6, 51, 53 have been amended to "induces IFN-g production". As indicated above, the Examiner has admitted that Applicants' specification is enabling for assaying the ability of the test compound to modulate the activity of an MSH4 polypeptide. Thus, this rejection as it pertains to claims 6, 50-51, 53, 57, 64-75, 78-84 has been rendered moot. Accordingly, Applicants request reconsideration and withdrawal of this §112, first paragraph rejection of claims 4, 6, 50-51, 53, 57, 64-75, and 78-84.

SUMMARY

In view of the above amendment, applicant believes the pending application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Dated: February 5, 2007

Respectfully submitted,

By _____

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APPENDIX A

lalign output for Human T-bet SEQ ID NO:1 vs. Mouse T-bet SEQ ID NO:3

[ISREC-Server] Date: Thu Nov 9 21:12:46 Europe/Zurich 2006

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resetting matrix to DNA ./wwwtmp/lalign/.27842.1.seq : 1608 nt

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989) 4:11-17
Human T-bet SEQ ID NO:1                              1608 nt vs.
Mouse T-bet SEQ ID NO:3                              1593 nt
scoring matrix: DNA, gap penalties: -14/-4
85.7% identity;         Global alignment score: 5950

               10        20        30        40        50        60
./wwwt ATGGGCATCGTGGAGCCGGGTTGCGGAGACATGCTGACGGGCACCGAGCCGATGCCGGGG
       :::::::::::::::::::: ::::::::::::::::: ::::::::::::::::::   :
Mouse  ATGGGCATCGTGGAGCCGGGCTGCGGAGACATGCTGACCGGCACCGAGCCGATGCC---G
               10        20        30        40        50

               70        80        90       100       110       120
./wwwt AGCGACGAGGGCCGGGCGCCTGGCGCCGACCCGCAGCACCGCTACTTCTACCCGGAGCCG
       :: :::::::::::::: ::: :: :: :::: ::::: :: : :::::: :: ::::::
Mouse  AGTGACGAGGGCCGGGGGCCCGGAGCGGACCAACAGCATCGTTTCTTCTATCCCGAGCCG
        60        70        80        90       100       110

              130       140       150       160       170       180
./wwwt GGCGCGCAGGACGCGGACGAGCGTCGCGGGGGCGGCAGCCTGGGGTCTCCCTACCCGGGG
       ::::: :::::: ::  ::: :: :::: ::  :::::::::::: : :::::: : :::
Mouse  GGCGCACAGGACCCGACCGATCGCCGCGCAGGTAGCAGCCTGGGGACGCCCTACTCTGGG
       120       130       140       150       160       170

              190       200       210       220       230       240
./wwwt GGCGCCTTGGTGCCCGCCCCGCCGAGCCGCTTCCTTGGAGCCTACGCCTACCCGCCGCGA
       :::::: :::::::: ::: ::::: : :::::::::::: ::: :::::::::::: ::
Mouse  GGCGCCCTGGTGCCTGCCGCGCCGGGTCGCTTCCTTGGATCCTTCGCCTACCCGCCCCGG
       180       190       200       210       220       230

              250       260       270       280       290       300
./wwwt CCCCAGGCGGCCGGCTTCCCCGGCGCGGGCGAGTCCTTCCCGCCGCCCGCGGACGCCGAG
        : :::: ::: ::::: ::::::  : ::::::: :::::::::::::::::  :: :::
Mouse  GCTCAGGTGGCTGGCTTTCCCGGGCCTGGCGAGTTCTTCCCGCCGCCCGCGGGTGCGGAG
       240       250       260       270       280       290

              310       320       330       340       350       360
./wwwt GGCTACCAGCCGGGCGAGGGCTACGCCGCCCCGGACCCGCGCGCCGGGCTCTACCCGGGG
       ::::::: ::: :  :: :::::: : ::::: :::::::::: :::::::::: :::
Mouse  GGCTACCCGCCCGTGGATGGCTACCCTGCCCCTGACCCGCGCGCGGGGCTCTACCCAGGG
       300       310       320       330       340       350

              370       380       390       400       410       420
./wwwt CCGCGTGAGGACTACGCGCTACCCGCGGGACTGGAGGTGTCGGGGAAACTGAGGGTCGCG
       ::::: ::::::::::  : ::::::::  ::::::::: ::::: ::::: ::::::
Mouse  CCGCGCGAGGACTACGCATTGCCCGCGGGGTTGGAGGTGTCTGGGAAGCTGAGAGTCGCG
       360       370       380       390       400       410

              430       440       450       460       470       480
./wwwt CTCAACAACCACCTGTTGTGGTCCAAGTTTAATCAGCACCAGACAGAGATGATCATCACC
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                :::: ::::::::::::::::::::::: :: :::::::::::::::::::::::::
Mouse           CTCAGCAACCACCTGTTGTGGTCCAAGTTCAACCAGCACCAGACAGAGATGATCATCACT
                420        430        440        450        460        470

                       490        500        510        520        530        540
./wwwt          AAGCAGGGACGGCGGATGTTCCCATTCCTGTCATTTACTGTGGCCGGGCTGGAGCCCACC
                ::::: :::::::: ::::::::::::::::: :: :: ::::::::::::::::::::
Mouse           AAGCAAGGACGGCGAATGTTCCCATTCCTGTCCTTCACCGTGGCCGGGCTGGAGCCCACA
                480        490        500        510        520        530

                       550        560        570        580        590        600
./wwwt          AGCCACTACAGGATGTTTGTGGACGTGGTCTTGGTGGACCAGCACCACTGGCGGTACCAG
                ::::: ::::::::::::::::: ::::::::::::::::::::::::::::::::::::
Mouse           AGCCATTACAGGATGTTTGTGGATGTGGTCTTGGTGGACCAGCACCACTGGCGGTACCAG
                540        550        560        570        580        590

                       610        620        630        640        650        660
./wwwt          AGCGGCAAGTGGGTGCAGTGTGGAAAGGCCGAGGGCAGCATGCCAGGAAACCGCCTGTAC
                :::::::::::::::::::::::::::: :: :::::::::::::: :::::: : ::
Mouse           AGCGGCAAGTGGGTGCAGTGTGGAAAGGCAGAAGGCAGCATGCCAGGGAACCGCTTATAT
                600        610        620        630        640        650

                       670        680        690        700        710        720
./wwwt          GTCCACCCGGACTCCCCCAACACAGGAGCGCACTGGATGCGCCAGGAAGTTTCATTTGGG
                :::::::: :::::::::::::: ::::: ::::::::::::::::::::::::::::::
Mouse           GTCCACCCAGACTCCCCCAACACCGGAGCCCACTGGATGCGCCAGGAAGTTTCATTTGGG
                660        670        680        690        700        710

                       730        740        750        760        770        780
./wwwt          AAACTAAAGCTCACAAACAACAAGGGGGCGTCCAACAATGTGACCCAGATGATTGTGCTC
                :: :::::::::::: :::::::::::::: :::::::::::::::::::::::: :: ::
Mouse           AAGCTAAAGCTCACCAACAACAAGGGGGCTTCCAACAATGTGACCCAGATGATCGTCCTG
                720        730        740        750        760        770

                       790        800        810        820        830        840
./wwwt          CAGTCCCTCCATAAGTACCAGCCCCGGCTGCATATCGTTGAGGTGAACGACGGAGAGCCA
                ::::: ::::: :::::::::::::::::::: ::::: :::::::: :: :::::::::
Mouse           CAGTCTCTCCACAAGTACCAGCCCCGGCTGCACATCGTGGAGGTGAATGATGGAGAGCCA
                780        790        800        810        820        830

                       850        860        870        880        890        900
./wwwt          GAGGCAGCCTGCAACGCTTCCAACACGCATATCTTTACTTTCCAAGAAACCCAGTTCATT
                ::::: :::::::  ::::: ::::: ::  ::::::::::::::: ::::::::::::
Mouse           GAGGCTGCCTGCAGTGCTTCTAACACACACGTCTTTACTTTCCAAGAGACCCAGTTCATT
                840        850        860        870        880        890

                       910        920        930        940        950        960
./wwwt          GCCGTGACTGCCTACCAGAATGCCGAGATTACTCAGCTGAAAATTGATAATAACCCCTTT
                :: ::::::::::::::: :: ::::: :::::::::::: :: :: :::::::::::
Mouse           GCAGTGACTGCCTACCAGAACGCAGAGATCACTCAGCTGAAAATCGACAACAACCCCTTT
                900        910        920        930        940        950

                       970        980        990       1000       1010       1020
./wwwt          GCCAAAGGATTCCGGGAGAACTTTGAGTCCATGTACACATCTGTTGACACCAGCATCCCC
                :::::::::::::::::::::::::::::::::::: :::::::::: :: ::  :::::
Mouse           GCCAAAGGATTCCGGGAGAACTTTGAGTCCATGTACGCATCTGTTGATACGAGTGTCCCC
                960        970        980        990       1000       1010

                      1030       1040       1050       1060       1070       1080
./wwwt          TCCCCGCCTGGACCCAACTGTCAATTCCTTGGGGGAGATCACTACTCTCCTCTCCTACCC
                :: :: :::::::::::::::::: : :::::::::: : :: ::: ::::: ::: ::
Mouse           TCGCCACCTGGACCCAACTGTCAACTGCTTGGGGGAGACCCCTTCTCACCTCTTCTATCC
              1020       1030       1040       1050       1060       1070

                      1090       1100       1110       1120       1130       1140
./wwwt          AACCAGTATCCTGTTCCCAGCCGCTTCTACCCCGACCTTCCTGGCCAGGCGAAGGATGTG
                :::::::::::::::::::::: ::::::::::::::::: :::::: : :::::: ::
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Mouse  AACCAGTATCCTGTTCCCAGCCGTTTCTACCCCGACCTTCCAGGCCAGCCCAAGGATATG
      1080      1090      1100      1110      1120      1130

             1150      1160      1170      1180      1190      1200
./wwwt GTTCCCCAGGCTTACTGGCTGGGGGCCCCCCGGGACCACAGCTATGAGGCTGAGTTTCGA
        :  : ::: :::::::::::::: : :: ::::: ::::: ::::: :: ::::: :::
Mouse  ATCTCACAGCCTTACTGGCTGGGGACACCTCGGGAACACAGTTATGAAGCGGAGTTCCGA
      1140      1150      1160      1170      1180      1190

             1210      1220      1230      1240      1250      1260
./wwwt GCAGTCAGCATGAAGCCTGCATTCTTGCCCTCTGCCCCTGGGCCCACCATGTCCTACTAC
        :: :: ::::::::::::  :: :: : :::::::::: :::::::  :: ::::::::
Mouse  GCTGTGAGCATGAAGCCCACACTCCTACCCTCTGCCCCGGGGCCCACTGTGCCCTACTAC
      1200      1210      1220      1230      1240      1250

             1270      1280      1290      1300      1310      1320
./wwwt CGAGGCCAGGAGGTCCTGGCACCTGGAGCTGGCTGGCCTGTGGCACCCCAGTACCCTCCC
        :: ::::: :: :::::::: :::::::::: ::::: ::::: :: :: ::::: :::
Mouse  CGGGGCCAAGACGTCCTGGCGCCTGGAGCTGGTTGGCCCGTGGCCCCTCAATACCCGCCC
      1260      1270      1280      1290      1300      1310

             1330      1340      1350      1360      1370      1380
./wwwt AAGATGGGCCCGGCCAGCTGGTTCCGCCCTATGCGGACTCTGCCCATGGAACCCGGCCCT
        :::::: :::: ::  :::::::::: :: ::::: :::::::::::::: :: ::::
Mouse  AAGATGAGCCCAGCTGGCTGGTTCCGGCCCATGCGAACTCTGCCCATGGACCCGGGCCTG
      1320      1330      1340      1350      1360      1370

             1390      1400      1410      1420      1430      1440
./wwwt GGAGGCTCAGAGGGACGGGGACCAGAGGACCAGGGTCCCCCCTTGGTGTGGACTGAGATT
        :::  :::::::: :: :::  :                 :::::: : ::::: ::::: :
Mouse  GGATCCTCAGAGGAACAGGGCTCCT------------CCCCCTCGCTGTGGCCTGAGGTC
      1380      1390      1400                  1410      1420

             1450      1460      1470      1480      1490      1500
./wwwt GCCCCCATCCGGCCGGAATCCAGTGATTCAGGACTGGGCGAAGGAGACTCTAAGAGGAGG
        :: :: ::: ::::::  :::: :: :::::::: :::::::::::: ::::::::::
Mouse  ACCTCCCTCCAGCCGGAGCCCAGCGACTCAGGACTAGGCGAAGGAGACACTAAGAGGAGG
        1430      1440      1450      1460      1470      1480

             1510      1520      1530      1540      1550      1560
./wwwt CGCGTGTCCCCCTATCCTTCCAGTGGTGACAGCTCCTCCCCTGCTGGGGCCCCTTCTCCT
        :  : ::::::::::::::::::: :::::::::: :: ::::::::::::::::::
Mouse  AGGATATCCCCCTATCCTTCCAGTGGCGACAGCTCCTCTCCCGCTGGGGCCCCTTCTCCT
        1490      1500      1510      1520      1530      1540

             1570      1580      1590      1600
./wwwt TTTGATAAGGAAGCTGAAGGACAGTTTTATAACTATTTTCCCAACTGA
       :::::::::::: : ::::: :::::::::: ::::::::::::::
Mouse  TTTGATAAGGAAACCGAAGGCCAGTTTTATAATTATTTTCCCAACTGA
        1550      1560      1570      1580      1590
```

Back to ISREC bioinformatics group home page

APPENDIX B

lalign output for Human T-bet SEQ ID NO:2 vs. Mouse T-bet SEQ ID NO:4

[ISREC-Server] Date: Thu Nov 9 21:13:42 Europe/Zurich 2006

./wwwtmp/lalign/.12900.1.seq : 535 aa

```
ALIGN calculates a global alignment of two sequences
 version 2.0uPlease cite: Myers and Miller, CABIOS (1989) 4:11-17
Human T-bet SEQ ID NO:2                              535 aa vs.
Mouse T-bet SEQ ID NO:4                              530 aa
scoring matrix: BLOSUM50, gap penalties: -14/-4
86.9% identity;         Global alignment score: 3326

               10        20        30        40        50        60
./wwwt MGIVEPGCGDMLTGTEPMPGSDEGRAPGADPQHRYFYPEPGAQDADERRGGGSLGSPYPG
       :::::::::::::::::: :::::.:::: :::.:::::::::  .:::.:.:::.:: :
Mouse  MGIVEPGCGDMLTGTEPMP-SDEGRGPGADQQHRFFYPEPGAQDPTDRRAGSSLGTPYSG
               10         20        30        40        50

               70        80        90       100       110       120
./wwwt GALVPAPPSRFLGAYAYPPRPQAAGFPGAGESFPPPADAEGYQPGEGYAAPDPRAGLYPG
       :::::: :.:::::..::::: :.:::::: :: ::::: :::: : .:: ::::::::::
Mouse  GALVPAAPGRFLGSFAYPPRAQVAGFPGPGEFFPPPAGAEGYPPVDGYPAPDPRAGLYPG
      60         70        80        90       100       110

              130       140       150       160       170       180
./wwwt PREDYALPAGLEVSGKLRVALNNHLLWSKFNQHQTEMIITKQGRRMFPFLSFTVAGLEPT
       ::::::::::::::::::::.::::::::::::::::::::::::::::::::::::::::
Mouse  PREDYALPAGLEVSGKLRVALSNHLLWSKFNQHQTEMIITKQGRRMFPFLSFTVAGLEPT
     120       130       140       150       160       170

              190       200       210       220       230       240
./wwwt SHYRMFVDVVLVDQHHWRYQSGKWVQCGKAEGSMPGNRLYVHPDSPNTGAHWMRQEVSFG
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
Mouse  SHYRMFVDVVLVDQHHWRYQSGKWVQCGKAEGSMPGNRLYVHPDSPNTGAHWMRQEVSFG
     180       190       200       210       220       230

              250       260       270       280       290       300
./wwwt KLKLTNNKGASNNVTQMIVLQSLHKYQPRLHIVEVNDGEPEAACNASNTHIFTFQETQFI
       ::::::::::::::::::::::::::::::::::::::::::::::.:::::.:::::::::
Mouse  KLKLTNNKGASNNVTQMIVLQSLHKYQPRLHIVEVNDGEPEAACSASNTHVFTFQETQFI
     240       250       260       270       280       290

              310       320       330       340       350       360
./wwwt AVTAYQNAEITQLKIDNNPFAKGFRENFESMYTSVDTSIPSPPGPNCQFLGGDHYSPLLP
       ::::::::::::::::::::::::::::::::::::.:::::.:::::::::::: .:::::
Mouse  AVTAYQNAEITQLKIDNNPFAKGFRENFESMYASVDTSVPSPPGPNCQLLGGDPFSPLLS
     300       310       320       330       340       350

              370       380       390       400       410       420
./wwwt NQYPVPSRFYPDLPGQAKDVVPQAYWLGAPRDHSYEAEFRAVSMKPAFLPSAPGPTMSYY
       ::::::::::::::: ::.. : ::::.::::::::::::::::.:::::::::. ::
Mouse  NQYPVPSRFYPDLPGQPKDMISQPYWLGTPREHSYEAEFRAVSMKPTLLPSAPGPTVPYY
     360       370       380       390       400       410

              430       440       450       460       470       480
./wwwt RGQEVLAPGAGWPVAPQYPPKMGPASWFRPMRTLPMEPGPGGSEGRGPEDQGPPLVWTEI
```

```
       :::.:::::::::::::::::::.::.::::::::::.:: :.:: .:    . : .: :.
Mouse  RGQDVLAPGAGWPVAPQYPPKMSPAGWFRPMRTLPMDPGLGSSEEQG----SSPSLWPEV
     420       430       440       450       460           470

               490       500       510       520       530
./wwwt APIRPESSDSGLGEGDSKRRRVSPYPSSGDSSSPAGAPSPFDKEAEGQFYNYFPN
       . ..:: :::::::::.::::.:::::::::::::::::::::::.::::::::::
Mouse  TSLQPEPSDSGLGEGDTKRRRISPYPSSGDSSSPAGAPSPFDKETEGQFYNYFPN
         480       490       500       510       520       530
```

Back to ISREC bioinformatics group home page